REMARKS

Claims 58-108 are presently pending in this matter. In the instant Amendment, Claims 58 and 76 have been amended, and Claims 59-60, 64, 66-71, 73, 78, 81-92, 94, 98-104, and 108 have been canceled, without prejudice. Support for amended Claims 58 and 76 can be found generally throughout the instant Specification, and in the Claims 1-57 as originally filed.

Drawings

The Examiner has acknowledged the substitute drawings Applicants previously submitted are acceptable. Applicants thank the Examiner for this acknowledgement.

The Invention is Definite

Claims 58, 61-63, 65, 72, 74-77, 79-80, 92-93, 95-97, and 105-107 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner has asserted the use of the phrase "bending domain" in Claim 58 renders the Claims vague and indefinite because, in the Examiner's opinion, a review of the instant Specification does not identify a basis for this term, even though it is a term of the transcription factor art. Thus, it appears to the Examiner that the term "binding" was intended instead of "bending".

Applicants respectfully traverse this rejection. Claim 58 has been amended to recite the phrase "binding domain" in order to correct this typographical error. Hence, in light of this amendment, Claim 58 and Claims dependent thereto are clearly definite and supported, and this rejection is obviated.

The Invention is Novel

Claims 58, 61-63, 65, 92-93, 95-97 and 105-107 have been rejected under 35 U.S.C. § 102(e) as being anticipated by the teachings of U.S. Patent 5,650,298 awarded to Bujard *et al.* (the '298 patent). The Examiner has asserted the '298 patent teaches a system for regulating expression of eukaryotic genes using components of the Tet repressor/operator/inducer system of prokaryotes. More specifically, the Examiner believes the '298 patent teaches a system in which transcription of a nucleotide sequence operably linked to at least one tet operator sequence is stimulated by a tetracycline (Tc) – controllable transcriptional activator fusion protein (referred to herein as tTA), which is comprised of two polypeptides. Moreover, the Examiner contends that one of the polypeptides is a (full length) Tet repressor (TetR; e.g., a Tn10-derived tetR), which binds to tet operator sequences in the absence, but not the presence of Tc. The Examiner has asserted that the second polypeptide directly or indirectly activates transcription in eukaryotic cells (col. 1-2). The Examiner also believes that the second polypeptide can be a domain (e.g. dimerization domain), which recruits a transcriptional activator (e.g. an endogenous transcriptional activator) to interact with the tTA fusion protein by protein-protein interaction (e.g., a non-covalent interaction.).

Furthermore, the Examiner has asserted that the '298 patent teaches a system comprising the tTA and a Tet operator sequence (the regulatory sequence the tTA binds to, which comprises SEQ ID NO:1), a minimal promoter comprising at least a portion of the CMV IE promoter or Tk promoter (both of which comprises a TATA box) and a gene, all operably linked reading on an expression cassette, wherein binding of the tTA activates transcription (col. 12-14 and 62-63).

It is the position of the Examiner that the teachings of the '298 patent read on the instantly claimed bispecific chimeric molecule. Initially, the Examiner believes that the fusion protein of TetR with a second polypeptide that indirectly activates transcription by recruiting an endogenous transcriptional activator is done through binding, and that the endogenous transcriptional activator is characteristic of at least a physiological state (the activation of the gene(s) regulated by that endogenous transcriptional activator). Moreover, the Examiner is of the opinion that the absence of that endogenous transcriptional activator means that the genes normally regulated by that activator are not regulated. Consequently, the Examiner believes the lack of activation is a physiopathological situation.

Applicants respectfully traverse this rejection. Amended Claim 58 is directed towards, *inter alia*, a bispecific chimeric molecule comprising a DNA binding domain capable of binding selectively to a defined DNA sequence, a regulatory domain capable of binding specifically to a transactivator, a transrepressor or a transactivating or transrepressing complex, "*...and an arm consisting of from 5 to 30 amino acids that links said DNA binding domain with said regulatory domain* (emphasis added)." (Amended Claim 58). Support for the arm can readily be found on page 16, lines 13-28 and on page 17, lines 1-23 of the instant Specification, wherein Applicants explain:

> The DNA binding domain and the transactivator-binding domain are generally linked to each other through an arm. This arm generally consists of a peptide ***which confers sufficient flexibility for the two domains of the molecules of the invention to be functional autonomously.*** This peptide is generally composed of uncharged amino acids, which do not interfere with the activity of the molecules of the invention, such as for example glycine, serine, tryptophan, lysine or proline. The arm generally comprises 5 to 20 amino acids. Examples of peptide arms which can

be used for the construction of the molecule of the invention are for example:

- GGGSGGGSGGGS (SEQ ID No. 5)
- PKPSTPPGSS (SEQ ID No. 6) whose coding sequence is CCCAAGCCCAGTACCCCCCCAGGTTCTTCA (SEQ ID No. 6).

Preferred examples of molecules according to the invention are especially the following molecules:

a) ScFv-tag-Hinge-TET or Cro (Figure 5A)

This type of molecule comprises:... - a peptide arm of SEQ ID No. 6 (Hinge).....

This passage makes clear that a bispecific chimeric molecule of the instant Invention comprises *inter alia*, a peptide arm, and that the terms "arm" and "hinge" are interchangeable. Furthermore, Example 3 on pages 42-44 of the instant Specification discloses a the construction of nucleic acid sequences that encode, *inter alia*, a bispecific molecule of the present invention that comprises a hinge, Example 5 discloses the expression of such sequences, and Example 8 discloses that such molecules, e.g. TET19, TET02, which comprise a hinge, perform as Applicants expected.

Pursuant to MPEP § 706.02, "...for anticipation under 35 U.S.C. § 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present." Since the '298 patent does not teach a chimeric molecule having hinge, it is respectfully submitted that amended Claim 58 and Claims dependent thereto are directed towards novel subject matter, and should be allowed to issue.

The Invention is Unobvious

Claims 58, 61-63, 65, 72, 74, 79, 92-93, 95-97, and 105-107 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the '298 patent in view of Hupp *et al.* (Regulation of Specific DNA Binding Function of p53 (Cell 71:875-886 (1992)), and the teachings of U.S. Patent 5,892,020 to Mezes *et al.* (the '020 patent).

In making this rejection, the Examiner has admitted that the '298 patent neither teaches that the domain in tTA which binds to a transactivator as being an antibody, specifically a single chain antibody, nor that the DNA-binding domain is at the C-terminus and the transactivator-binding domain is at the N-terminus. However, the Examiner has asserted that the '298 patent teaches a system for regulatory expression of eukaryotic genes using components of the Tet repressor/operator/inducer system of prokaryotes, in which transcription of a nucleotide sequence operably linked to at least one tet operator sequence is stimulated by a tetracycline (Tc) – controllable transcription activator fusion protein comprising two polypeptides. (referred to herein as tTA). The first polypeptide is a (full length) Tet repressor (TetR, e.g., a Tn10 – derived tetR), which binds to tet operator sequences in the absence but not the presence of Tc. The second polypeptide allegedly activates transcription in eukarytic cells directly or indirectly (col. 1-2 of the '298 patent). Moreover, the Examiner believes the second polypeptide can be a domain (e.g. a dimerization domain), which recruits a transcriptional activator (e.g. an endogenous transcriptional activator) to interact with the tTA fusion protein by protein – protein interaction (e.g., a non-covalent interaction) (col. 2 of the '298 patent). The Examiner is of the opinion that the teachings of the '298 patent read on the claimed bispecific chimeric molecule of the instant Invention because the fusion protein of TetR with a second polypeptide that indirectly activates transcription by recruiting an

endogenous transcriptional activator is characteristic of at least a physiological state (the activation of the gene(s) regulated by that endogenous transcriptional activator), and the absence of that endogenous transcriptional activator means that the genes normally regulated by that activator are not and thus that lack of activation is a physiopathological situation.

In addition, the Examiner has asserted that the '298 patent teaches a system comprising the tTa and a Tet operator sequence (the regulatory sequence the tTA binds to, which comprises SEQ ID NO:1), a minimal promoter comprising at least a portion of the CMV IE promoter or Tk promoter (both of which comprises a TATA box) and a gene, all operably linked reading on an expression cassette, wherein binding of the tTA activates transcription (col. 12-14 and 62-63).

The Examiner has also asserted that Hupp *et al.* teach the monoclonal antibody pAb421, which binds p53 and activates p53 (abstract; Results section). It is the Examiner's belief that p53 is taught as being a cellular protein involved in sequence-specific binding/transcriptional activation in cancer (page 875).

Furthermore, the Examiner is of the opinion that the '020 patent teaches construction of single-chain antibodies from multi-chain antibodies, which allow for the construction of an antibody fragment which has the specificity and avidity of a whole antibody but are smaller in size, and can be easily expressed by expression vectors (col. 1-6 of the '020.

In light of the Examiner's beliefs and assumptions with respect to the teachings of the '298 patent, the '020 patent, and Hupp *et al.*, it is the Examiner's opinion that it would have been obvious for one of ordinary skill in the art at the time the instant

Invention was made to modify the tTA system taught in the '298 patent by using single chain monoclonal antibody as the domain that binds to the transactivator, as taught by the '020 patent, using as a basis for the antibody pAB421, which Hupp *et al.* teaches binds to p53, a transactivation protein involved in cancer. Furthermore, the Examiner believes the '298 patent teaches that it is within the ordinary skill in the art to use any domain in tTA which indirectly interacts with a transcriptional activator by binding, the '020 patent teaches it is within the ordinary skill in the art to construct single-chain antibodies from multi-chain antibodies which have the specificity and avidity of a whole antibody and which can be expressed in expression vectors, and Hupp *et al.* teach that a specific antibody that binds to p53, an endogenous transactivator involved in cancer, which binding activates p53.

Furthermore, the Examiner believes one would have been motivated to combine these references as the Examiner has done in making this rejection to obtain the "expected" benefit of making a tTA that activates the same genes as p53, which is involved in cancer, as taught by the combined teachings of the cited references. It is the position of the Examiner that based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and an absence of evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Applicants respectfully traverse this rejection. As explained above, the teachings of the '298 patent do not anticipate the subject matter of amended Claim 58 and Claims dependent thereto. Indeed, there is no mention of a peptide arm between the two domains that confer sufficient flexibility to the molecule in order to permit each of the protein domains to act autonomously. Likewise, the teachings Hupp *et al.* are unrelated

to the teachings of the '298 and '020 patents, as well as instant Invention. In particular, Hupp *et al.* disclose a monoclonal antibody for p53 that may modulate the DNA binding activity of p53. Indeed, on page 883, Hupp *et al.* make clear that:

> ...p53 requires activating factors to confer effective sequence-specific DNA binding activity. Targeted conformational changes within the C terminus introduced by monoclonal antibody binding...appear to be mechanisms whereby DNA binding is activated.

Yet, as the Examiner has admitted, the '298 patent neither teaches nor suggests the use of an antibody in the tetracycline (Tc)-controllable transcriptional activator fusion protein described therein, and the '020 patent, which teaches the construction of single chain antibodies, is silent regarding the use of such antibodies in a chimeric protein such as a bispecific chimeric molecule of the present invention. Indeed, it is made clear in lines 61-66 of column 6 of the '020 patent that:

> The multivalent single chain antibodies of the present invention provide unique benefits for use in ***diagnostics*** and ***therapeutics***. The use of multivalent single chain antibodies afford a number of advantages over the use of larger fragments or entire antibody molecules. ***They reach their target tissue more rapidly, and are cleared more quickly from the body.***

(Col. 6, lines 61-66 of the '020 patent (emphasis added).

In light of the great disparity among the teachings of the references cited by the Examiner, as well as with the instant Invention, it is respectfully submitted that ***Applicants' disclosure*** has motivated the Examiner to combine these references as he has done. Hence, the Examiner has impermissibly utilized hindsight in an unsuccessful attempt to reconstruct Applicants' Invention from this combination of references. The Examiner cannot rely on hindsight to arrive at a determination of obviousness. *In re*

Fritch, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). The Court of Appeals for the Federal Circuit has stated that "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicant's disclosure." [*Interconnect Planning Corporation v. Fed.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). Thus, in the light of the above, it is respectfully submitted that this rejection be withdrawn, the Claims as amended be allowed to issue.

Furthermore, Claims 58, 61-63, 65, 75-77, 92-93, and 105-107 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the teachings of the '298 patent in view of the teachings of the U.S. Patent 5,990,274 to Whitlow *et al.* (the '274 patent). The Examiner's interpretations of the teachings of the '298 patent are set forth above. Also, the Examiner believes the '298 patent teaches that the linkage between components of the fusion protein can be done using any means that preserves the function of each polypeptide. However, the Examiner has admitted that the '298 patent ***does not*** teach the use of an arm consisting of from about 5 to 20 amino acids, such as SEQ ID NO:5 in linking the DNA binding domain the second polypeptide. The Examiner has also asserted that the '274 patent teaches the use of a peptide linker (18-50 amino acids in length) for connecting polypeptide constituents together into a fusion polypeptide (abstract) in order to provide greater stability and decreased susceptibility to aggregation (abstract).

It is the position of the Examiner that it would have been obvious to one of ordinary skill in the art at the time the instant Invention was made to use the peptide

linkers taught by the '274 patent, or any other linkers known in the art, such as SEQ ID NO:5, in making the fusion tTA protein taught in the '298 patent because the '298 patent also teaches making fusion proteins between a DNA binding domain and a polypeptide that binds with a transactivator.

Applicants respectfully traverse this rejection. As explained above, the '298 patent is teaches or suggests ***nothing*** with respect to the use of a hinge or arm in the molecule described therein. Furthermore, the Examiner has asserted that the '274 patent teaches the use of a peptide linker (18-50 amino acids in length) for connecting polypeptide constituents together into a fusion polypeptide (abstract) in order to provide "*...**greater stability and decreased susceptibility to aggregation*** (abstract)." Yet, as explained page 16 of the instant Specification, an arm is used in a bispecific molecule of the present invention in order to confer "***sufficient flexibility***" for the two domains of the molecule so that the domains can function "***autonomously***". Hence, contrary to the Examiner's assertions, neither the teachings of the '298 patent nor the teachings of the '274 patent would motivate or suggest to one of ordinary skill in the art to combine their teachings as the Examiner has done in making this rejection. Hence, Applicants respectfully submit that just as above, the Examiner has utilized impermissible hindsight in making this rejection, and the Claims as amended should be allowed to issue.

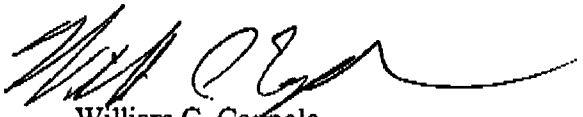
Fees

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. Early and favorable action on the Claims is earnestly solicited.

Respectfully submitted,



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